

(19) 世界知的所有権機関  
国際事務局



(43) 国際公開日  
2004年8月26日 (26.08.2004)

PCT

(10) 国際公開番号  
WO 2004/071503 A1

- (51) 国際特許分類<sup>7</sup>: A61K 31/195, 31/216, 31/405, A61P 31/12, 1/16, C07C 235/28, 235/76, 237/22, 251/38, C07D 209/20
- (74) 代理人: 津国 肇 (TSUKUNI, Hajime); 〒1050001 東京都港区虎ノ門1丁目22番12号 SVAX T S ビル Tokyo (JP).
- (21) 国際出願番号: PCT/JP2004/001498
- (81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) 国際公開日: 2004年2月12日 (12.02.2004)
- (25) 国際出願の言語: 日本語
- (26) 国際公開の言語: 日本語
- (30) 優先権データ:  
特願2003-034056 2003年2月12日 (12.02.2003) JP  
特願2003-272420 2003年7月9日 (09.07.2003) JP
- (84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) 出願人 (米国を除く全ての指定国について): 中外製薬株式会社 (CHUGAI SEIYAKU KABUSHIKI KAISHA) [JP/JP]; 〒1158543 東京都北区浮間5丁目5番1号 Tokyo (JP).
- (72) 発明者; および
- (75) 発明者/出願人 (米国についてのみ): 青木 雅弘 (AOKI, Masahiro). 加藤 秀之 (KATO, Hideyuki). 須藤 正幸 (SUDOH, Masayuki). 佃 拓夫 (TSUKUDA, Takuo). 増渕 みや子 (MASUBUCHI, Miyako). 川崎 健一 (KAWASAKI, Kenichi).
- 添付公開書類:  
— 国際調査報告書
- 2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: REMEDY FOR VIRAL DISEASE

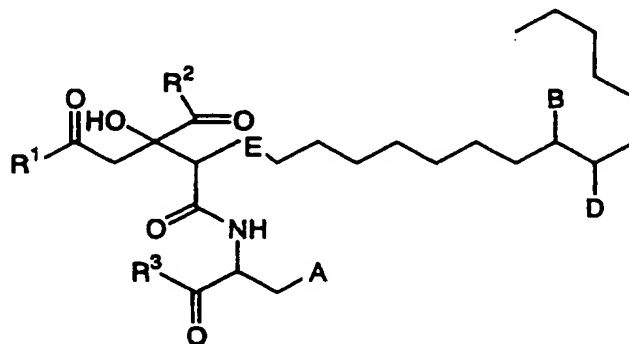
(54) 発明の名称: ウイルス治療薬

(57) Abstract: It is intended to provide a medicinal composition for preventing or treating viral infection. A medicinal composition containing a compound, which has an extremely potent anti-HCV activity and an HCV amplification inhibitory effect and shows little cytotoxicity *in vivo*, is highly useful as a preventive/remedy for HCV.

(57) 要約: 本発明は、ウイルス感染症を予防または治療するための医薬組成物の提供を目的とする。本発明の化合物は、非常に強い抗HCV活性及びHCVの増幅抑制効果を有し、かつ、インビロ細胞毒性については軽微であることから、本発明の化合物を含む医薬組成物は抗HCV予防/治療剤として極めて有用である。

# Claims

1. A pharmaceutical composition for preventing or treating viral infectious diseases comprising a compound represented by the following general formula (I):



5

(wherein

A represents a phenyl group substituted with -OX, or a 3-indolyl group;

10 X represents a hydrogen atom, a linear or branched alkyl group having 1 to 8 carbon atoms, a linear or branched alkenyl group having 2 to 8 carbon atoms, or a linear or branched alkynyl group having 2 to 8 carbon atoms;

15 B represents a hydrogen atom, a hydroxyl group, an oxo group, -N(R<sup>4</sup>)(R<sup>5</sup>), =N-OH, =N-OR<sup>6</sup> or a halogen atom;

20 R<sup>4</sup> and R<sup>5</sup> may be the same or different, and each represent a hydrogen atom, a linear or branched alkyl group having 1 to 6 carbon atoms, a linear or branched alkenyl group having 2 to 6 carbon atoms, or a linear or branched alkynyl group having 2 to 6 carbon atoms, or R<sup>4</sup> and R<sup>5</sup> together represent a 3 to 8 membered ring;

25 R<sup>6</sup> represents a linear or branched alkyl group having 1 to 8 carbon atoms (which may be substituted with an amino group which may be mono- or di-substituted with a linear or branched alkyl group having 1 to 4 carbon atoms);

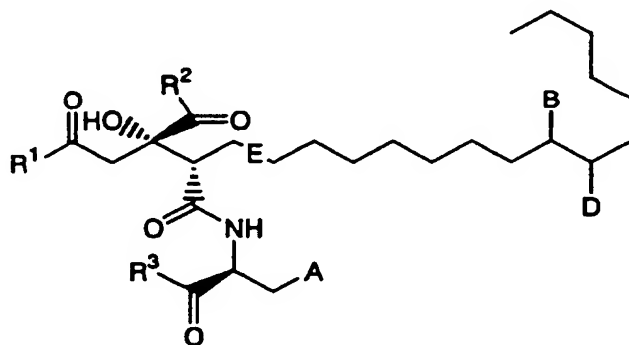
D represents a hydrogen atom or a hydroxyl group; bond E represents a single bond or double bond;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may be the same or different, and each

represent a hydrogen atom, a hydroxyl group, an amino group (which may be mono- or di-substituted with a linear or branched alkyl group having 1 to 4 carbon atoms), -OZ, a linear or branched alkyl group having 1 to 4 carbon atoms, a linear or branched alkenyl group having 2 to 4 carbon atoms, or a linear or branched alkynyl group having 2 to 4 carbon atoms; and,

Z represents a linear or branched alkyl group having 1 to 4 carbon atoms, a linear or branched alkenyl group having 2 to 4 carbon atoms, or a linear or branched alkynyl group having 2 to 4 carbon atoms) a prodrug thereof or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition according to claim 1 comprising the compound of formula (I) according to claim 1 represented by the following general formula (I'), a prodrug thereof or a pharmaceutically acceptable salt thereof:



(wherein A, B, D, bond E, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are the same as defined in claim 1).

3. The pharmaceutical composition according to claim 1 or 2 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt thereof wherein A represents a phenyl group substituted with -OX at position 4, X represents a hydrogen atom, a linear or

branched alkyl group having 1 to 8 carbon atoms, a linear or branched alkenyl group having 2 to 8 carbon atoms, or a linear or branched alkynyl group having 2 to 8 carbon atoms.

5

4. The pharmaceutical composition according to any one of claims 1 to 3 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt thereof, wherein B represents an oxo group, a hydrogen  
10 atom, a hydroxyl group or =N-OR<sup>6</sup>.

5. The pharmaceutical composition according to any one of claims 1 to 4 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt  
15 thereof, wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may be the same or different and each represent a hydroxyl group, an amino group, or -OZ (wherein Z represents a linear or branched alkyl group having 1 to 4 carbon atoms).

20 6. The pharmaceutical composition according to claim 1 or 2 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt thereof, wherein A represents a phenyl group substituted with -OX at position 4, X represents a hydrogen atom, a linear or  
25 branched alkyl group having 1 to 8 carbon atoms, a linear or branched alkenyl group having 2 to 8 carbon atoms or a linear or branched alkynyl group having 2 to 8 carbon atoms, B represents an oxo group, a hydroxyl group or =N-OR<sup>6</sup>, and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may be the same or different and  
30 each represent a hydroxyl group or -OZ (wherein Z represents a linear or branched alkyl group having 1 to 4 carbon atoms).

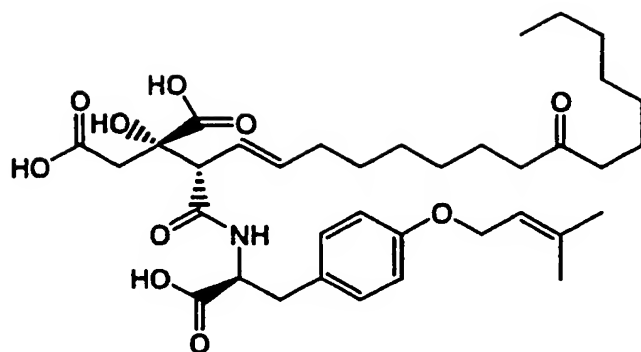
7. The pharmaceutical composition according to claim 6  
35 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt thereof, wherein X

represents a linear or branched alkyl group having 1 to 8 carbon atoms, a linear or branched alkenyl group having 2 to 8 carbon atoms or a linear or branched alkynyl group having 2 to 8 carbon atoms, B represents an oxo group or a hydroxyl group, and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> each represent a hydroxyl group.

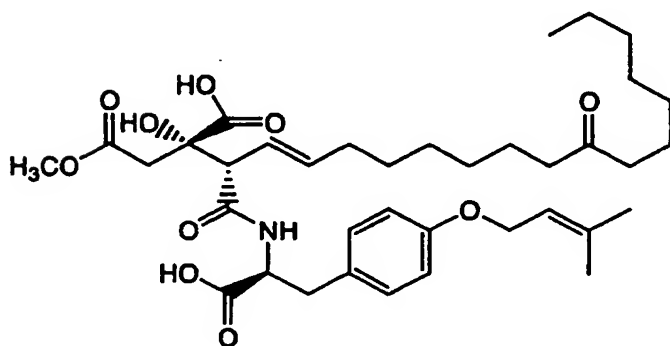
8. The pharmaceutical composition according to claim 1 or 2 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt thereof, wherein A represents a 3-indolyl group.

9. The pharmaceutical composition according to claim 8 comprising a compound of formula (I), a prodrug thereof or a pharmaceutically acceptable salt thereof, wherein B represents an oxo group or a hydroxyl group, and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> each represent a hydroxyl group.

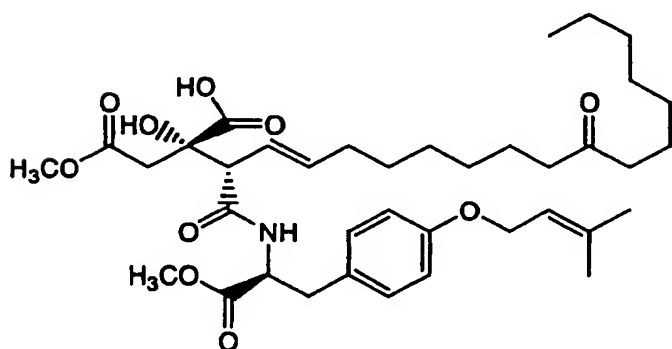
10. The pharmaceutical composition according to claim 1 or 2 comprising a compound of formula (I), a prodrug thereof of a pharmaceutically acceptable salt thereof, selected from the compounds indicated below.



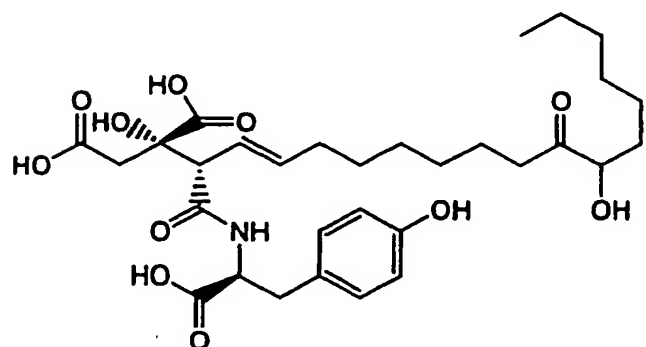
No.1



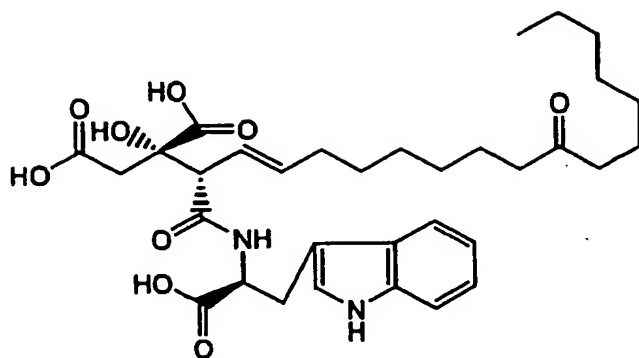
No.2



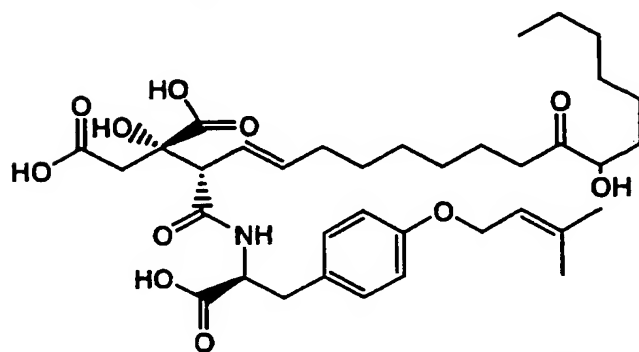
No.3



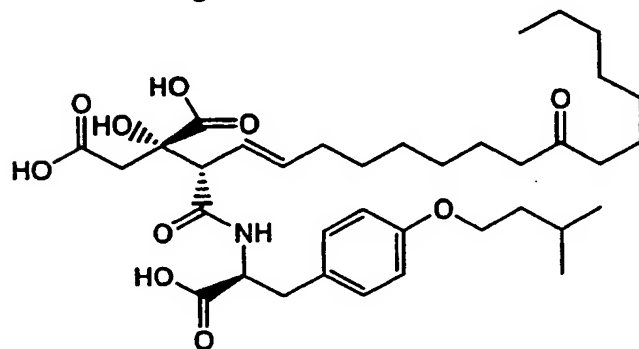
No.4



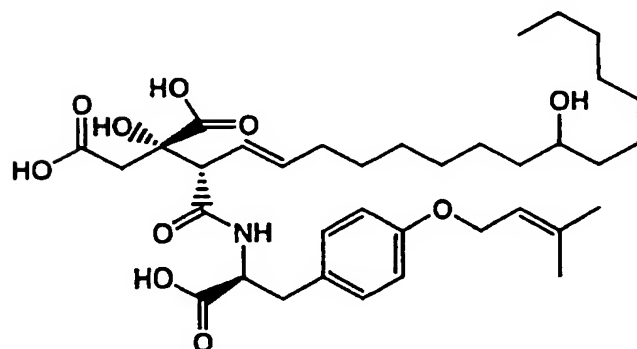
No.5



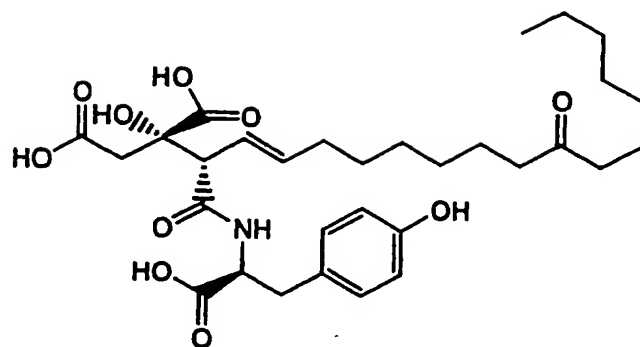
No.6



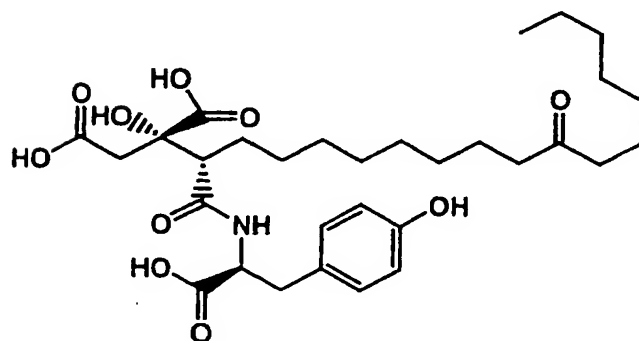
No.7



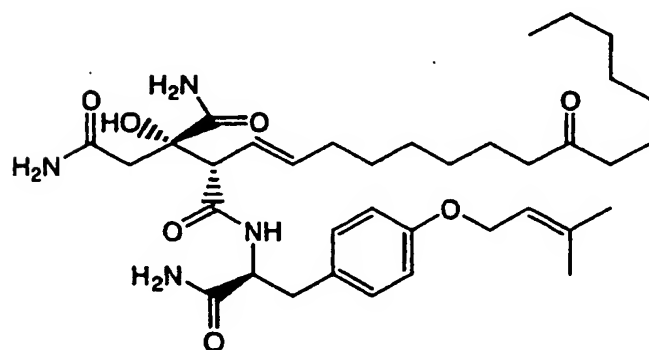
No.8



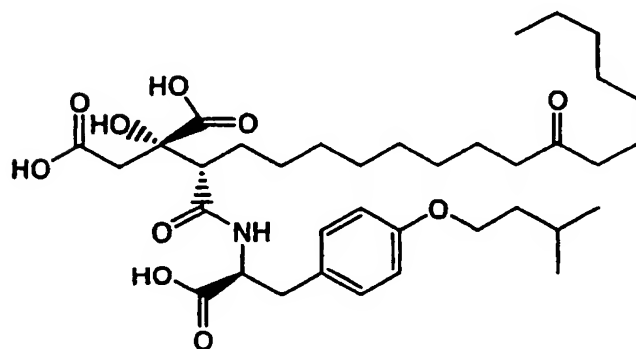
No.9



No.10

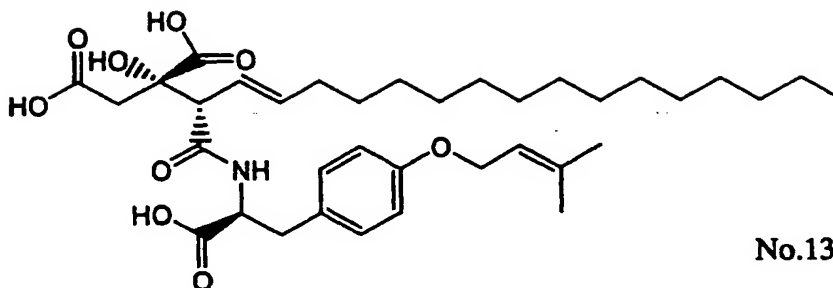


No.11

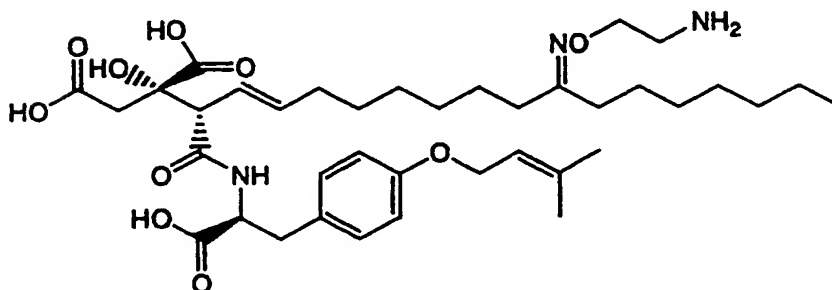


No.12



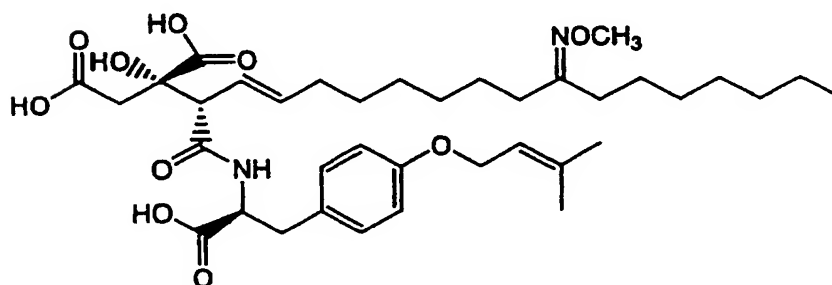


No.13



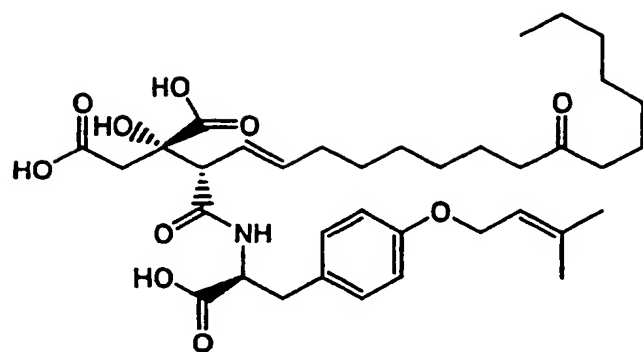
No.14

or

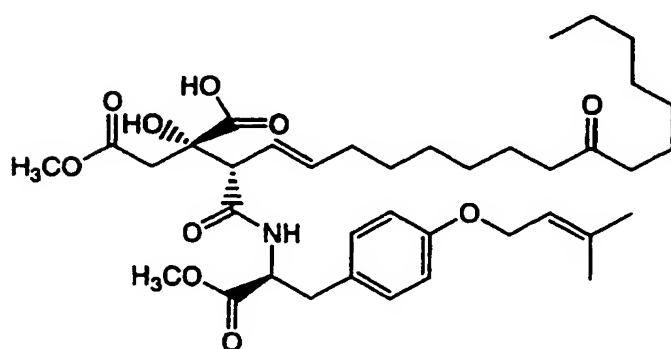


No.15

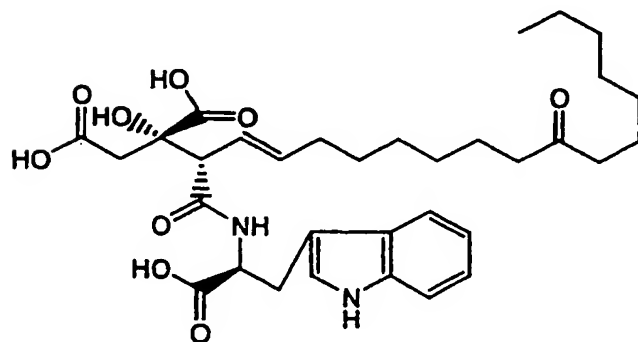
11. The pharmaceutical composition according to claim 1  
or 2 comprising a compound of formula (I), a prodrug  
thereof or a pharmaceutically acceptable salt thereof,  
5 selected from the compounds indicated below.



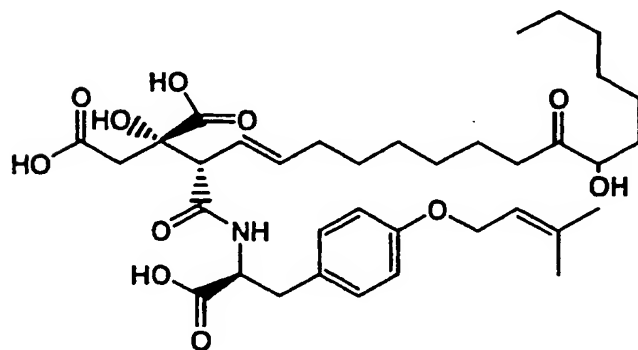
No.1



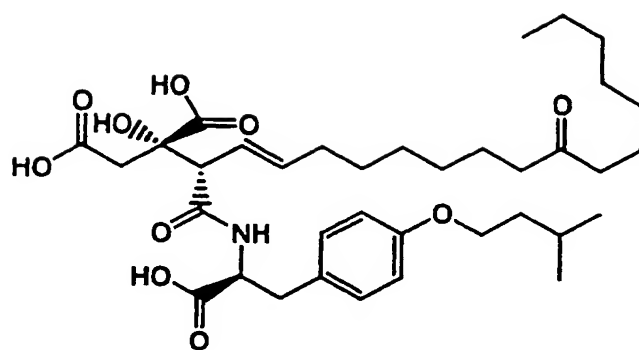
No.3



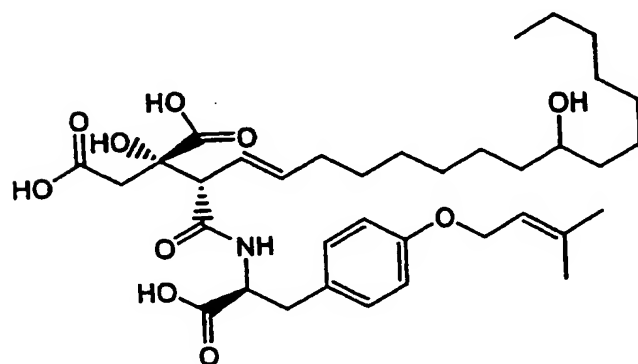
No.5



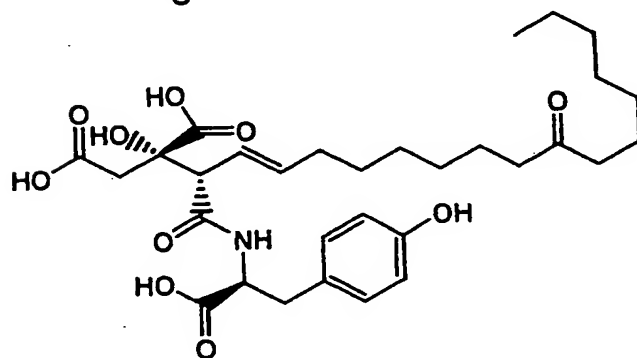
No.6



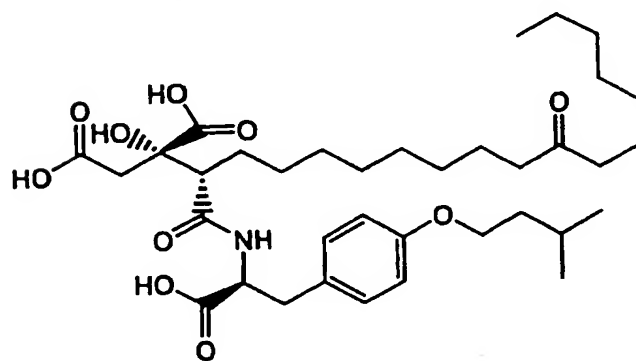
No.7



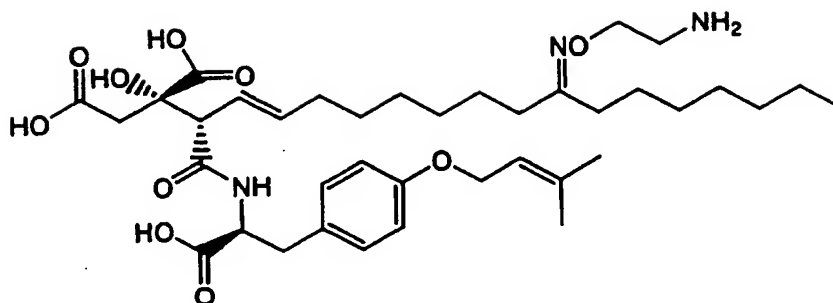
No.8



No.9

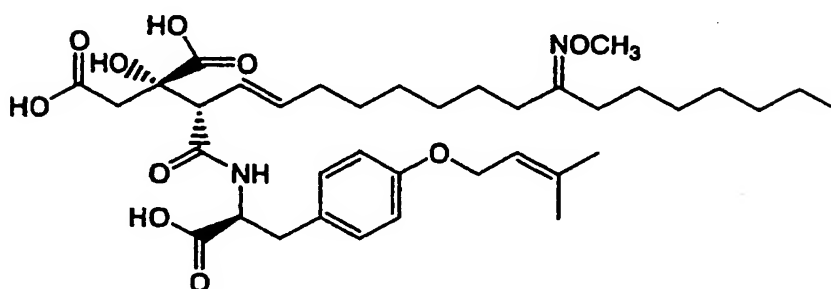


No.12



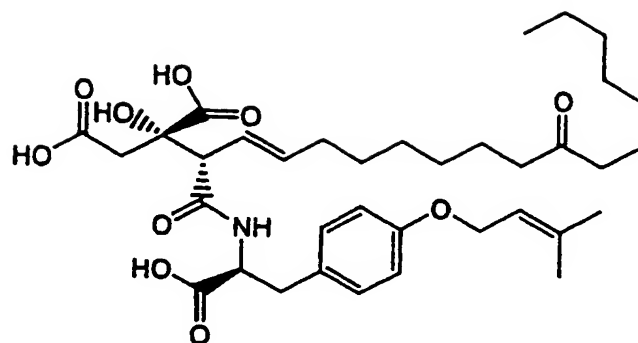
No.14

or

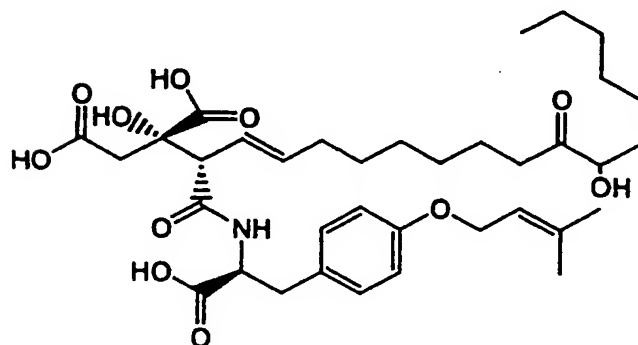


No.15

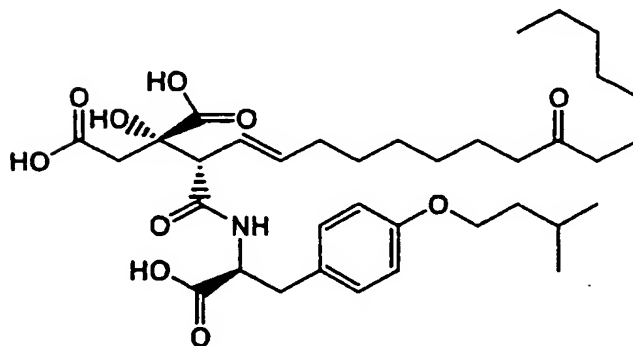
12. The pharmaceutical composition according to claim 1  
or 2 comprising a compound of formula (I), a prodrug  
5 thereof or a pharmaceutically acceptable salt thereof,  
selected from the compounds indicated below.



No.1

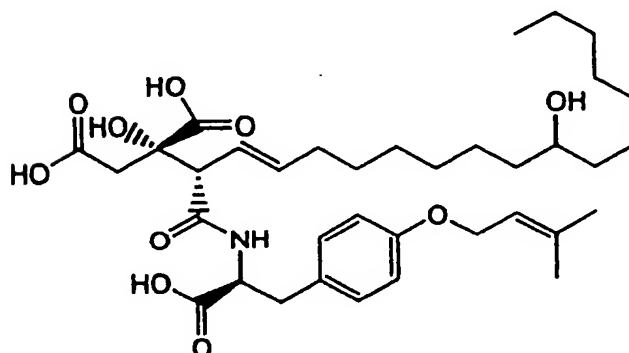


No.6



No.7

or

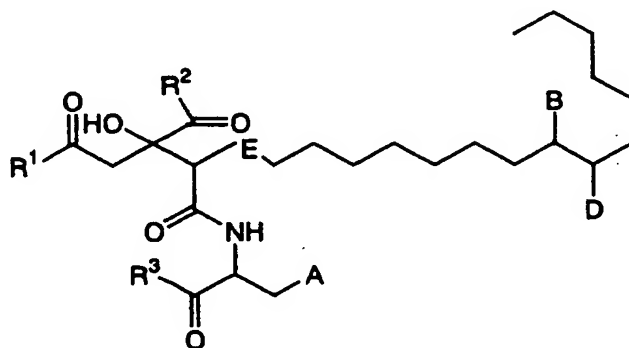


No.8

13. The pharmaceutical composition according to any one  
of claims 1 to 12, wherein the viral infectious disease is  
5 HCV infection.

14. The pharmaceutical composition according to claim 13, wherein the HCV infection is hepatitis C.

15. A compound represented by the following general  
5 formula (I):



(wherein

A represents a phenyl group substituted with -OX;

X represents a hydrogen atom, a linear or branched  
10 alkyl group having 1 to 8 carbon atoms, a linear or  
branched alkenyl group having 2 to 8 carbon atoms, or a  
linear or branched alkynyl group having 2 to 8 carbon  
atoms;

B represents a hydrogen atom, a hydroxyl group, an  
15 oxo group, -N(R<sup>4</sup>)(R<sup>5</sup>), =N-OH, =N-OR<sup>6</sup> or a halogen atom;

R<sup>4</sup> and R<sup>5</sup> may be the same or different, and each  
represent a hydrogen atom, a linear or branched alkyl  
group having 1 to 6 carbon atoms, a linear or branched  
alkenyl group having 2 to 6 carbon atoms, or a linear or  
20 branched alkynyl group having 2 to 6 carbon atoms, or R<sup>4</sup>  
and R<sup>5</sup> together represent a 3 to 8 membered ring;

R<sup>6</sup> represents a linear or branched alkyl group  
having 1 to 8 carbon atoms (which may be substituted with  
an amino group which may be mono- or di-substituted with a  
25 linear or branched alkyl group having 1 to 4 carbon  
atoms);

D represents a hydrogen atom or a hydroxyl group;

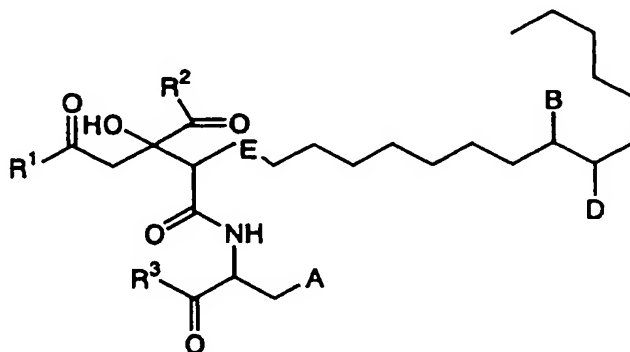
bond E represents a single bond or double bond;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may be the same or different, and each

represent a hydrogen atom, a hydroxyl group, an amino group (which may be mono- or di-substituted with a linear or branched alkyl group having 1 to 4 carbon atoms), -OZ, a linear or branched alkyl group having 1 to 4 carbon atoms, a linear or branched alkenyl group having 2 to 4 carbon atoms, or a linear or branched alkynyl group having 2 to 4 carbon atoms; and,

Z represents a linear or branched alkyl group having 1 to 4 carbon atoms, a linear or branched alkenyl group having 2 to 4 carbon atoms, or a linear or branched alkynyl group having 2 to 4 carbon atoms, with the proviso that the case in which A is a phenyl group substituted with -OX at the p position, X is a 2-isopentenyl group or a hydrogen atom, B is an oxo group, D is a hydrogen atom, E represents a double bond, and all of R<sup>1</sup> to R<sup>3</sup> are a hydroxyl group, and the case in which A is a phenyl group substituted with -OX at position p, X is a 2-isopentenyl group, B is an oxo group, D is a hydrogen atom, bond E represents a double bond, and all of R<sup>1</sup> to R<sup>3</sup> are a methoxy group are excluded) a prodrug thereof or a pharmaceutically acceptable salt thereof.

16. A compound represented by the following general formula (I):



(wherein

A represents a phenyl group substituted with -OX;  
X represents a hydrogen atom, a linear or branched

alkyl group having 1 to 8 carbon atoms, a linear or branched alkenyl group having 2 to 8 carbon atoms, or a linear or branched alkynyl group having 2 to 8 carbon atoms;

5           B represents a hydrogen atom, a hydroxyl group, an oxo group,  $-N(R^4)(R^5)$ ,  $=N-OH$ ,  $=N-OR^6$  or a halogen atom;

$R^4$  and  $R^5$  may be the same or different, and each represent a hydrogen atom, a linear or branched alkyl group having 1 to 6 carbon atoms, a linear or branched  
10 alkenyl group having 2 to 6 carbon atoms, or a linear or branched alkynyl group having 2 to 6 carbon atoms, or  $R^4$  and  $R^5$  together represent a 3 to 8 membered ring;

$R^6$  represents a linear or branched alkyl group having 1 to 8 carbon atoms (which may be substituted with  
15 an amino group which may be mono- or di-substituted with a linear or branched alkyl group having 1 to 4 carbon atoms);

          D represents a hydrogen atom or a hydroxyl group;  
          bond E represents a single bond or double bond;

20            $R^1$ ,  $R^2$  and  $R^3$  may be the same or different, and each represent a hydrogen atom, a hydroxyl group, an amino group (which may be mono- or di-substituted with a linear or branched alkyl group having 1 to 4 carbon atoms),  $-OZ$ ,  
a linear or branched alkyl group having 1 to 4 carbon  
25 atoms, a linear or branched alkenyl group having 2 to 4 carbon atoms, or a linear or branched alkynyl group having 2 to 4 carbon atoms; and,

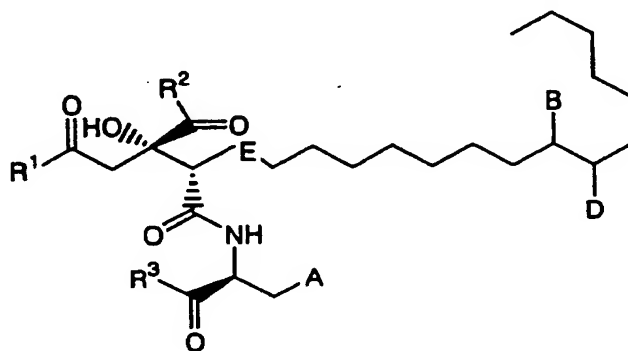
          Z represents a linear or branched alkyl group having 1 to 4 carbon atoms, a linear or branched alkenyl  
30 group having 2 to 4 carbon atoms, or a linear or branched alkynyl group having 2 to 4 carbon atoms, with the proviso that the case in which A is a phenyl group substituted with  $-OX$  at position p and X is a hydrogen atom, and the case in which A is a phenyl group substituted with  $-OX$  at  
35 position p, X is a 2-isopentenyl group, B is an oxo group, D is a hydrogen atom, bond E indicates a double bond, and



all of  $R^1$  to  $R^3$  are a hydroxyl group or a methoxy group are excluded)  
a prodrug thereof or a pharmaceutically acceptable salt thereof.

5

17. The compound of formula (I) according to claim 15 or 16 represented by the following general formula (I'), a prodrug thereof or a pharmaceutically acceptable salt thereof:

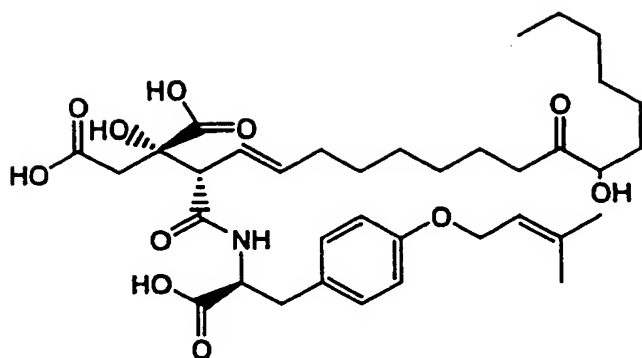


10

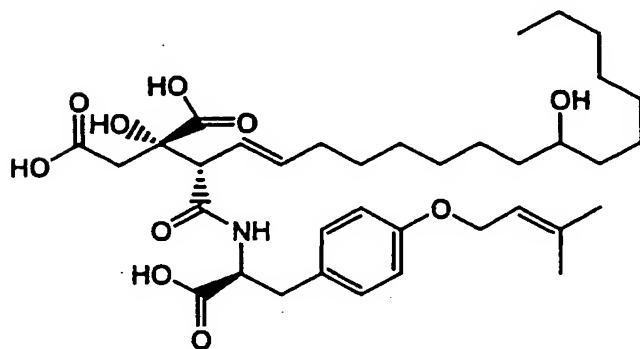
(wherein  $X$ ,  $B$ ,  $D$ , bond  $E$ ,  $R^1$ ,  $R^2$  and  $R^3$  are the same as described in claim 15).

18. The compound of formula (I) according to claims 15 to 17, a prodrug thereof or a pharmaceutically acceptable salt thereof, wherein  $X$  represents a linear or branched alkyl group having 1 to 8 carbon atoms, a linear or branched alkenyl group having 2 to 8 carbon atoms or a linear or branched alkynyl group having 2 to 8 carbon atoms, and  $B$  represents a hydroxyl group, an oxo group or  $=N-OR^6$ .

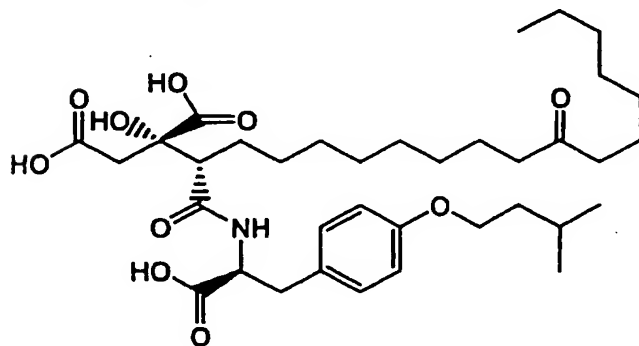
19. The compound of formula (I) according to any one of claims 15 to 18 represented by the following formula, a prodrug thereof or a pharmaceutically acceptable salt thereof.



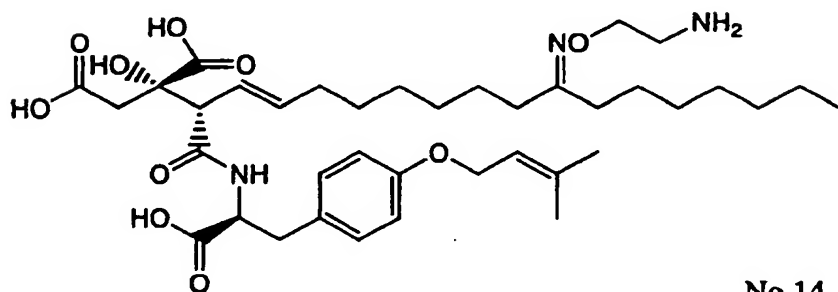
No.6



No.8

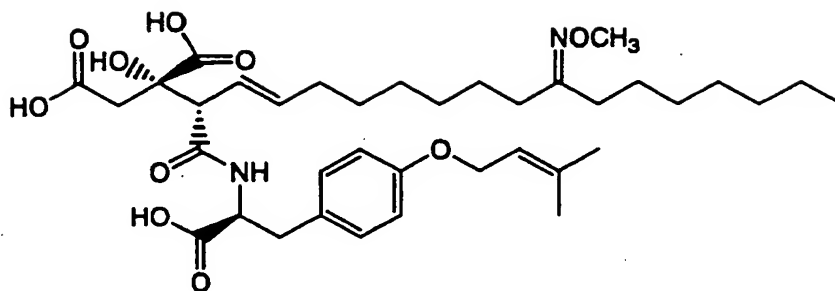


No.12



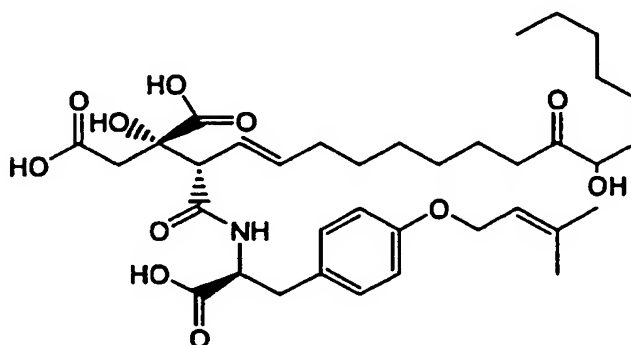
No.14

or



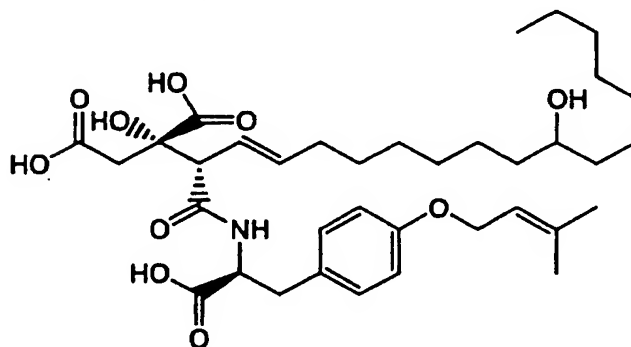
No.15

20. The compound of formula (I) according to any one of  
claims 15 to 18 represented by the following formula, a  
5 prodrug thereof or a pharmaceutically acceptable salt  
thereof.



No.6

or



No.8

21. A pharmaceutical composition comprising a compound  
10 of formula (I) according to any one of claims 15 to 20, a  
prodrug thereof or a pharmaceutically acceptable salt  
thereof.

22. The pharmaceutical composition according to claim

21 for preventing or treating of viral infectious diseases.

23. The pharmaceutical composition according to claim  
22, wherein the viral infectious disease is HCV infection.

5

24. The pharmaceutical composition according to claim  
23, wherein the HCV infection is hepatitis C.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ ~~FADED~~ TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**